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(54) Title: TREATMENT OF NON-ULCER DYSPEPSIA WITH BISMUTH SALTS

(57) Abstract

Treatment of non-ulcer dyspepsia associated with *Campylobacter pyloridis* infection by the administration of bismuth salts. The administration of bismuth salts in association with antibiotics has been found to be particularly efficacious. A pharmaceutical composition for use in the performance of the present invention is also disclosed.

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TREATMENT OF NON-ULCER DYSPEPSIA WITH BISMUTH SALTS

BACKGROUND ART

This invention relates to a method of treating non-ulcer dyspepsia. In the past bismuth compounds have been used in the treatment of dyspepsia arising from peptic ulcers. However, there has been previously no recognised therapy for the treatment of non-ulcer dyspepsia. Non-ulcer dyspepsia has not been widely recognised in the past as being a single disease process and has been considered as comprising various disorders with such names as "nervous dyspepsia", "irritable bowel syndrome", "gastritis", and also "post-cholecystectomy syndrome". Non-ulcer dyspepsia is characterised by epigastric discomfort, burning or pain, abdominal distention, bloating, belching or burping, nausea, and frequently it is said that the ingestion of food can precipitate such symptoms.

The treatment of this disorder has, until now, been non-specific, empirical and generally inadequate.

It has now been discovered that a new class of spiral bacteria reside in the stomach of humans. These bacteria have been found to be closely associated with the presence of gastritis. It has now also been found that the symptoms of non-ulcer dyspepsia are closely related to the presence of the newly discovered spiral bacteria. These bacteria are Campylobacter-like bacteria, currently called Campylobacter pyloridis.

While the use of bismuth salts to treat ulcers has been known, their utility in the treatment of non-ulcer dyspepsia has not been suspected previously. The symptoms of the two conditions are generally different, but may at times overlap. The diagnosis is made endoscopically.

DISCLOSURE OF THE INVENTION

The present invention relates to a method of treating non-ulcer dyspepsia in patients suffering from the said non-ulcer dyspepsia, comprising administering to the said patients an effective amount of a pharmaceutically acceptable bismuth salt.

A preferred bismuth compound for the treatment of

non-ulcer dyspepsia is tripotassium dicitratobismuthate. This is also known as De-Nol (Registered Trade Mark). Other bismuth compounds known for the treatment of ulcer and other diseases may also be used in the present invention. Ideally, the bismuth salt is administered orally for a period of at least four (4) weeks and may be administered alone in an adequate dose or in combination with other antibiotics.

It has further been found that the treatment of non-ulcer dyspepsia with bismuth salt is enhanced by the concurrent administration of an antibiotic.

Particularly suitable antibiotics may be chosen from the classes consisting of β-lactams, such as penicillins; macrolide antibiotics; tetracycline antibiotics and nitro-imidazole sulfones. From within these classes Amoxycillin, Erythromycin, Tetracycline and Tinidazole have been found to be particularly efficacious.

Another aspect of the invention comprises a pharmaceutical composition comprising a pharmaceutically acceptable bismuth salt, an antibiotic and pharmaceutically acceptable carrier or diluent.

Preferably the bismuth salt is tripotassium dicitrato-bismuthate.

The most preferable antibiotics are selected from the classes specified above. In particular, the β-lactam antibiotics. Most preferably, the antibiotic is Amoxycillin.

The pharmaceutical composition is preferably presented in a form suitable for peroral administration, such as liquid, tablet or capsule form.

BEST MODE OF CARRYING OUT THE INVENTION

The invention will now be further described with reference to the following examples.

Example 1

27 Patients suffering from non-ulcer dyspepsia associated with C.pyloridis infection were treated with the bismuth salt, tripotassium dicitrato-bismuthate, known under the registered Trade Mark "De-Nol". All patients were administered 107.7mg De-Nol four times daily. Of the 27, 6 were treated with De-Nol alone. Of these it was found that

40% were completely clear of dyspepsia after 1 month and 60% after two months. The remaining patients were treated with combinations of De-Nol and the antibiotics Amoxycillin and Tinidazole. 250mg Amoxycillin was administered four times daily for four weeks and 1gm Tinidazole was administered daily for 10 days. The results were 95% clear completely within 4 weeks. Rebiopsy of the completely clear patients, performed 2 weeks after the four week treatment ceased, showed that the patients remained completely clear.

Trials with Amoxycillin alone indicate that Amoxycillin has no appreciable effect in the treatment of dyspepsia.

Example 2

The following pharmaceutical formulation is proposed for use in the performance of the present invention:

Tablet formulation

tripotassium dicitrato-bismuthate	107.7mg
amoxycillin	250 mg
magnesium stearate	10 mg
maize starch	20 mg

Flavouring substances may be added as required.

It will be clear to those skilled in the art that other formulations falling within the scope of the present invention are possible, and that the invention is therefore not restricted to the above formulation.

CLAIMS

1. A method of treating non-ulcer dyspepsia in patients suffering from non-ulcer dyspepsia associated with Campylobacter pyloridis infection, comprising administering to said patients an effective amount of a pharmaceutically acceptable bismuth salt.

2. A method according to claim 1 wherein the bismuth salt is tripotassium dicitrato-bismuthate.

3. A method according to claim 1 wherein the bismuth salt is administered in conjunction with one or more antibiotics.

4. A method according to claim 3 wherein the antibiotics are selected from the β-lactam antibiotics, macrolide anitbiotics, tetracycline antibiotics and nitro-imidazole sulfones.

5. A method according to claim 4 wherein the antibiotics are selected from Amoxycillin, Tinidazole, Erythromycin and Tetracycline.

6. A method according to claim 5 wherein Amoxycillin and Tinidazole are administered in conjunction with the bismuth salt.

7. A method of treating non-ulcer dyspepsia in patients suffering from non-ulcer dyspepsia, substantially as hereinbefore described with reference to the examples.

8. A pharmaceutical composition comprising a pharmaceutically acceptable bismuth salt, an antibiotic and a pharmaceutically acceptable carrier or diluent.

9. A pharmaceutical composition according to claim 8 wherein the bismuth salt is tripotassium dicitrato-bismuthate.

10. A pharmaceutical composition according to either one of claims 8 or 9 wherein the antibiotic is a β-lactam antibiotic.

11. A pharmaceutical formulation according to claim 10 wherein the antibiotic is Amoxycillin.

12. A pharmaceutical formulation substantially as hereinbefore described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 86/00106

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [5]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[4] A61K 31/29, 31/43

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K 31/29, 27/00
US Cl.	514/503

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AU : IPC A61K 31/29, 33/24; Australian Classification 87.16-0

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
X	AU,A, 89503/82 (GIST-BROCADES N.V.) 31 March 1983 (31.03.83) See pages 1,10 and examples 1-3	(1)
X	AU,B, 65432/69 (440535) (EXPORT DRUGS COMPANY) 15 July 1971 (15.07.71) See page 3 lines 20-27	(1)
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X	AU,B, 53539/69 (438147) (BROWN) 22 October 1970 (22.10.70) See page 9 lines 7-10 and examples XIV, XV	(1)
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X	AU,B, 44545/79 (521699) 30 August 1979 (30.08.79) See pages 2-3, 17-26	(1)
X	FR,A, 2073254 (SYNTHELABO) 1 October 1971 (01.10.71) See page 1 lines 23-32	(1)

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
6 June 1986 (06.06.86)	(01-07-86) 01 JULY 1986
International Searching Authority	**Signature of Authorized Officer**
Australian Patent Office	J.P. PULVIRENTI

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X	FR,A, 2029402 (BREIVE et al) 23 October 1970 (23.10.70) See page 1 lines 1-15	(1)
X	US,A, 4153685 (SERFONTEIN) 8 May 1979 (08.05.79) See column 1 lines 14-19 and columns 8-13	(1)
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X	Martindale, 'The Extra Pharmacopoeia', 28th Edition, published 1982, by The Pharmaceutical Press (London), See pages 927 to 930	(1)

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 86/00106

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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